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DEFINING RESTENOSIS

Restenosis After Coronary Angioplasty: An Overview

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Despite substantial basic and clinical efforts to address the problem of restenosis after percutaneous coronary intervention, effective preventive therapies have not yet been developed. Nevertheless, the accumulated information has provided much insight into the process of restenosis in addition to allowing standards to be developed for adequate clinical trials.

The pathophysiology of restenosis increasingly appears to be distinct from that of primary atherosclerosis. Restenosis involves elastic recoil, incorporation of thrombus into the lesion and fibrocellular proliferation in varying degrees in different patients. Lack of an animal model that satisfactorily mimics restenosis is a major impediment to further understanding of the process. Clinical studies are hampered by difficulties in finding a single unifying definition of restenosis and by variable methods of reporting follow-up. Reporting of clinical outcomes of all patients in angiographic substudies would allow a more satisfactory interpretation of the results of clinical trials. Current noninvasive test results are not accurate enough to substitute for angiographic and clinical outcome data in intervention trials.

In the majority of observational studies, only diabetes and unstable angina have emerged as consistently associated with restenosis; whereas most of the standard risk factors for atherosclerosis have a less consistent relation. Disappointingly, the new atherectomy and laser technologies have not affected restenosis rates. The one possible exception is coronary stenting, as a result of the larger luminal diameter achieved by the placement of the stent.

***In conclusion*, although substantial continued effort is necessary to explore the basic aspects of cellular proliferation and mechanical alteration of atherosclerotic vessels, attention to the principles of clinical trials and observation are required to detect the impact of risk factors and interventions on the multifactorial problem of restenosis. Adequate sample sizes, collection of clinical and angiographic outcomes and factorial study designs hold promise for unraveling this important limitation of percutaneous intervention.**

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The topic of restenosis after coronary angioplasty has continued to arouse great interest as the volume of interventional procedures performed continues to increase. Recent data document an increase from 100,000 angioplasty procedures in 1985 to 300,000 in 1989. The addition of newer technologies into the therapeutic armamentarium has further intensified the need to develop approaches to reduce the occurrence of restenosis. Despite the tremendous amount of basic and clinical research addresssing this problem, this overview must begin with the simple summary statement that an approach to restenosis that is definitely proved to reduce its occurrence has not yet been developed. The remainder of this report focuses on a review of developments in our understanding of the process of restenosis and the approaches that may lead to a reduction in restenosis rates.

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Pathophysiology

Unstable atherosclerotic plaque. Primary atherosclerotic plaque contains a complex mixture of smooth muscle cells, fibrous tissue and cholesterol. Restenotic lesions are much more fibrous in nature, with few cholesterol pools. Despite the limitations of most previous studies examining the influence of traditional risk factors for atherosclerosis on restenosis risk, only in the case of diabetes has a major effect been observed. However, increasing evidence is accumulating that the instability of angina relates closely to the risk of adverse events after angioplasty, implicating the unstable atherosclerotic plaque with accompanying thrombotic factors as a major culprit. This difference in plaque composition may also explain the rarity of recurrent infarction as a presenting manifestation of restenosis because myocardial infarction is generally believed to result from fissuring of an

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atherosclerotic plaque in an area overlying a lipid pool (1). The fibrous nature of the restenotic plaque may protect it against rupture.

Animal model of atherosclerosis. Unfortunately, a suitable animal model of restenosis capable of simulating the human process has not been found. Characteristics of an ideal animal model of atherosclerosis include the presence of minimal genetic variability within the model, an accelerated time frame for the induction and development of lesions and histologic and morphologic similarity between the animal lesion and the complex human atherosclerotic plaque. Additional desirable features include anatomy that approximates human arteries with regard to dimensions and configuration, the capacity to withstand multiple procedures and low costs for feeding, instrumentation and management of the animal. Consistent development of high grade stenoses and occlusions has been limited to selected rabbit, swine and nonhuman primate models (2,3). Rabbit models, while economical, generally involve production of extreme hyperlipidemia, with plaque histologic studies revealing foam cells with little fibrosis or calcification. The vessel caliber and distal vessel topology are also not suitable for testing interventional strategies (4,5). Nonhuman primates can yield atherosclerotic lesions similar to human lesions, but are more difficult to manage, expensive to maintain and require prolonged induction and development time. Miniature and micro swine models have recently been developed for interventional research. In the Yucatan micro swine, complex lesions resembling human plaques have developed after balloon denudation and a hypercholesterolemic diet (6). However, even this model has the drawbacks of a high attrition rate and lack of peripheral vascular access, and the model necessitates the study of peripheral rather than coronary arteries.

Role of animal studies. Given the inadequacies of each of these animal models, the decision to proceed from animal testing to human investigation remains difficult. The necessity of developing safety and feasibility data from animal models is well recognized, but the choice of a particular model does not currently have a sound theoretic or practical base. A further difficult issue is whether success in one animal model is enough to justify human study or whether multiple animal models should be used. Currently, we believe that animal studies are most useful to define the possibility that intimal proliferation can be impeded by a particular therapy, but that this type of study should not lead to confidence that a similar result should be anticipated in complex human atherosclerotic plaque.

Reporting Restenosis Rates

The pioneering work of Serruys et al. (7) has led to a clearer understanding of the issues involved in determining restenosis rates. Essential to the development of comparable standards is the concept that clinical outcome measures must be integrated with the measurement of absolute changes in the dimensions of the vessel lumen. Recent reports (7,8) illustrate the difficulties in using traditional or visual methods of assessment, with significant overestimation of lesion severity by 15% to 25% as compared with quantitative methods, further obscuring the likelihood of detecting real changes in vessels undergoing angioplasty. These reports also suggest that visual assessment is highly inaccurate in the midrange of diameter stenosis estimates (25% to 75%) in which procedural success or failure is being determined.

Standards for assessing results of angioplasty. In evaluating the results of angioplasty relative to other therapeutic alternatives and for developing clinically effective approaches to the problem of restenosis, three measurements are helpful. 1) The severity of the stenosis before the procedure should be carefully measured (constituting the baseline measurement). 2) Measurement of the degree of obstruction in the early postprocedure period is essential (yielding the "acute result"). Although a preliminary report from Emory University (9) indicated that optimization of postangioplasty results had little impact on restenosis rates in a series of 2,444 patients, the follow-up angiographic rate was 52%, leading to a substantial risk of statistical bias (see Statistical Approaches). Data from the M-HEART study (10) suggest that although procedural success can be achieved in the overwhelming majority of patients, the desired degree of stenosis reduction will be realized in only 75% of the successful procedures.

3) A preliminary report by Rensing et al. (11) suggested that in addition to changes occurring over prolonged periods during follow-up, more immediate changes occur. They described the phenomenon whereby 50% of the theoretic maximal gain is lost immediately after angioplasty secondary to elastic recoil of the vessel. This effect was most pronounced in the left anterior descending coronary artery and was considered not to be due to coronary spasm. Therefore, the determination of the postprocedure result should be made after allowing a brief period for the process of elastic recoil to become evident. Finally, the result at a designated follow-up point 4 to 6 months after the procedure, when the remodeling process will be completed in the majority of patients, provides the critical comparative measure (thus determining long-term success or failure) (7,12).

Objective quantification of angioplasty results. In reporting the impact of a therapy on clinical outcome, both the minimal luminal diameter and the luminal diameter relative to the reference vessel diameter should be coupled with event rates. Alternatively, to evaluate therapies designed to prevent the anatomic process of restenosis, the difference between the immediate postangioplasty result and the follow-up result should be quantified using an objective measure such as videodensitometry or an automated edge-tracing device. Kalbfleisch et al. (13) compared the results of automated quantitative angiography with caliper measurements of percent diameter stenosis. They found that overestimation of noncritical stenoses and underestimation of

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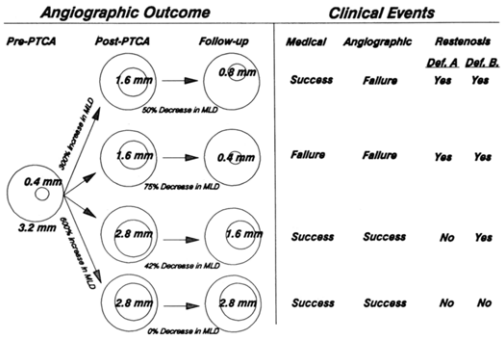


Figure 1. Examples of four cases involving interventional intracoronary technology. The reference diameter remains constant at 3.2 mm for all examples. In example 1, an immediate improvement in the minimal luminal diameter (MLD) of 300% results in a lumen of 1.6 mm (50% diameter stenosis). A modest encroachment of 0.8 mm results in a 50% decrease in minimal luminal diameter and a significant residual stenosis (75% diameter stenosis). In example 2, further encroachment leads to a 75% decrease in minimal luminal diameter (88% diameter stenosis) and recurrent angina. Restenosis occurs in both cases with use of both definition (Def.) A (>50% stenosis at follow-up) and definition B (>0.72 mm decrease in minimal luminal diameter from postprocedure to follow-up). In example 3, an improved initial result (a 600% improvement in minimal luminal diameter) coupled with a similar degree of encroachment during the follow-up period as in example 1 results in a minimal luminal diameter at follow-up of 1.6 mm (50% diameter stenosis). Restenosis occurs according to definition B, whereby a decrease of 0.8 mm in minimal luminal diameter is present, but there is no restenosis if definition A is used. In example 4, initial excellent results are maintained with the absence of restenosis by either definition.

critical stenoses occur frequently and that the measurements have poor overall reproducibility. The authors (13) concluded that because the use of calipers does not overcome the limitations of visual estimation of stenosis severity, this method cannot be recommended for clinical practice.

Measurements required for definition of restenosis. Several examples are given in Figure 1, illustrating the difficulty in using a definition of restenosis based on differences in "percent stenosis" alone. These examples hold the reference diameter constant for illustration purposes. In many cases, the reference diameter undergoes changes of similar magnitude to the minimal luminal diameter. The use of percent diameter stenosis then is dependent on two factors, varying independently and sometimes in opposite directions from each other, leading to an underestimation of the actual change in stenosis severity. To obviate these problems, we recommend that in addition to percent stenosis, absolute measurements should also be reported, either minimal luminal diameter (mm) or cross-sectional area (mm^2), to describe changes in vessel dimensions when the process of intimal proliferation is described.

Variables for reporting results of angioplasty. On the basis of this thought process, we suggest that the results of all intravascular interventional technologies be reported in terms of three variables. 1) The clinical outcomes of death, myocardial infarction, symptomatic angina and recurrence of ischemia as documented by functional testing for provokable ischemia should be reported. 2) The anatomic result before treatment, immediately after treatment and at long-term follow-up should be ascertained. 3) The difference between the immediate and long-term results should be quantified to estimate the overall restenosis effect. This measure ideally should be adjusted for changes occurring in the normal or reference portions of the vessel.

Angiographic assessment of intimal proliferation and procedural success. Reiber et al. (14) have taken an important step forward by proposing a standard for a quantitative angiographic definition of intimal proliferation. They suggested that only changes >0.72 mm in minimal luminal diameter represent a "true" change in the vessel geometry. This finding was derived from measurements made at disparate times under basal conditions, demonstrating that 0.72 mm represented twice the standard deviation of the difference of duplicate measurements. None of the patients in their study (14) underwent angioplasty before the measurements. Other work by this group (15) showed similar variability in the reference diameter (at 120 days, mean differences of −0.36 mm for the stenosis and −0.30 for the reference diameter), thus rendering the use of percent diameter stenosis somewhat questionable for the purpose of estimating the degree of intimal proliferation. The use of the preceding definition (change >0.72 mm) avoids reconciliation of the dynamic changes occurring in the reference diameter (7). Despite the obvious limitations suggested by these observations, binary restenosis rates can be reported, although continuous measurements of the absolute change in vessel dimensions remain the most sensitive method of comparing different groups of patients.

As noted previously, the data from which this quantitative reference standard was developed were acquired under basal conditions in patients who did not undergo coronary angioplasty before the measurements were obtained. Addi-

tional studies are needed to confirm the validity of this approach and whether an interaction may exist between the use of absolute dimensions (mm or mm^2) and the vessel dilated (for example, left anterior descending coronary artery diagonal branches versus right coronary artery marginal branches) or the absolute size of the vessel (1 to 2 vs. 3 to 4 mm). Detailed analyses of qualitative criteria of angiographic appearance to define a successful procedure have not been conducted, but such analyses comparing the initial angiographic appearance with long-term outcome are essential for understanding the determinants of a successful treatment strategy. A further area of investigation is whether angiographic criteria alone are sufficient for declaring procedural success or whether demonstration of reversal of ischemia or other metabolic abnormalities as determined by techniques such as thallium-201 scintigraphic studies or positron emission tomography will be useful. Until the necessary anatomic and clinical variables have been identified and standardized, the most relevant definition of restenosis will remain elusive.

If a binary variable for restenosis is to be utilized, a useful construct is to evaluate the presence or absence of progression of vessel encroachment using definitions that exceed the error of the technique. Despite these intellectually appealing observations, a report by Gurley et al. (16) provides disturbing documentation that additional standardization of methodology is required. They reported that reproducibility of quantitative angiography can be substantially altered by operator-dependent variables used in the identification and selection of both the projection and the frame.

Statistical Issues

The issue of random error: false positive and false negative results. Inadequate attention to several important statistical issues has hampered progress in the investigation of factors affecting restenosis and approaches to its prevention. One such issue is random error, which is essentially attributable to sampling variation, a factor strongly influenced by study design (for example, sample size) and statistical characteristics of the estimator (for example, variance). Two types of error can result from random sampling variation when making statistical inferences. First, the null hypothesis may be rejected when it is actually true, thus causing a false positive study. Alternatively, the null hypothesis may be accepted when the converse is true, leading to a false negative study.

In studies of restenosis, sample sizes for a particular outcome are often inadequate, potentially leading to the incorrect premise of a negative study (type II error). Another possible problem occurs when multiple statistical comparisons are made during the analysis phase of a study. In this instance, any association found may be entirely due to chance, thus producing a false positive result (type I error). Methods of adjusting for this potential source of error include adjusting the required p value for significance (Bonferroni correction), limiting comparisons according to the "rule of 10s" (one comparison for every 10 end points) or validation of the study results in a second entirely independent sample. In particular, validation in an independent sample provides significant strength for any association found.

The issue of differential rates of follow-up and coronary angiography. A major issue in studies evaluating restenosis stems from differential rates of follow-up. If the change in obstruction from the postprocedure result to a follow-up study is the best measure of restenosis, then the measurement must be made at follow-up evaluation. Unfortunately, coronary angiography is not a procedure that can be performed on all patients after angioplasty for a combination of technical, medical, social and economic reasons. The dropout of patients from repeat angiography does not occur with equal frequency across the spectrum of symptom classes because patients without symptoms, with a presumably lower rate of restenosis, are less likely to return for restudy. Patients who die, presumably with a higher restenosis rate, are unable to return. This problem, with selective and incomplete follow-up study, could be addressed on several levels to reduce statistical bias and increase the clinical relevance of results.

At the most basic level, the outcome of patients who do not return for coronary angiography can be classified in one of three ways. The patient's outcome could be having restenosis or having no restenosis or the patient's data could be excluded from the analysis group. Occasionally, an effort is made to improve the results by carrying the process one step further and determining the symptomatic status of the patient at the time when angiography was scheduled. A common policy is to consider an asymptomatic patient as having no restenosis. Because the reported restenosis rate in asymptomatic patients is between 10% and 32%, such an assumption can lead to a systematic underestimation of the true restenosis rate. Conversely, excluding these patients altogether and using data from those patients followed up angiographically only can lead to an overestimation of the true restenosis rate. Similar problems should be recognized in the case of patients who die or have an intercurrent myocardial infarction without repeat angiography. Exclusion of these patients is likely to result in a systematic underestimation of the true restenosis rate.

Addressing the problem of incomplete angiographic follow-up. A superior method for estimating the true restenosis rate would be to categorize the patient as carefully as possible for the probability of restenosis based on available clinical factors. Thus, knowing the proportion of patients without follow-up angiography in each symptom class (asymptomatic, atypical or typical symptoms) and the restenosis rates in the patients undergoing repeat angiography in each class, a better estimate of the "true" restenosis rate for the patients under study should be possible.

We have used data from the Coronary Artery Descriptors and Restenosis (CADRes) Project, an ongoing project at

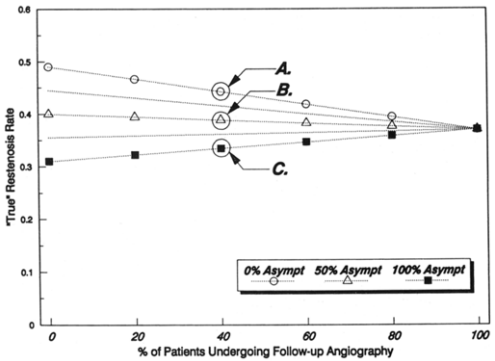


Figure 2. The problem resulting from selective and incomplete angiographic follow-up after angioplasty is demonstrated in this family of curves. Data presented here were derived from the CADRes population in which 85% angiographic follow-up was obtained. In this study the overall restenosis rate in patients followed up angiographically was 37%. However, to understand the effect of assumptions made concerning patients without follow-up angiography, this observed overall rate should be viewed as a weighted average of the restenosis rate observed for asymptomatic (31%) and that observed for symptomatic (49%) patients. The considerable difference in these two rates emphasizes the substantial variation that can occur in overall restenosis rates depending on the proportion of asymptomatic and symptomatic patients represented in a given population. **Examples A, B and C** are based on a group of patients with a 40% rate of angiographic follow-up and an observed restenosis rate of 37% among the patients with follow-up. In **example A** it is assumed that all patients without angiographic follow-up are symptomatic (that is, 0% are asymptomatic [Asympt]). If restenosis in the patients not followed up is assumed to occur at the 49% rate attributable to symptomatic patients, the estimated ("true") overall restenosis rate for the entire group would be 44%; that is, the estimated overall restenosis rate = ([0.37 × 0.40] + [0.49 × 0.60]).

In **example B** it is assumed that 50% of the patients not followed up are symptomatic and 50% are asymptomatic. In this case, it is assumed that 50% of the patients not followed up have the restenosis rate of 49% attributable to symptomatic patients and the remaining 50% have the 31% rate of restenosis attributable to asymptomatic patients. Under these assumptions, the estimated ("true") overall restenosis rate for the entire group would be 39%; that is, the estimated overall restenosis rate = ([0.37 × 0.40] + [0.49 × 0.30] + [0.31 × 0.30]).

In **example C** it is assumed that 100% of patients not followed up angiographically are asymptomatic. The patients without follow-up are then assumed to have restenosis at the 31% rate attributable to the asymptomatic patients. This results in an estimated ("true") overall restenosis rate for the entire group of 33%; that is, the estimated overall restenosis rate = (0.37 × 0.40) + (0.31 × 0.60).

Thus, in these three examples, despite the same observed restenosis rate (37%) in angiographically followed up patients, the estimated restenosis rate for the entire group ranges from 33% to 44%, depending on the assumptions made about the patients without angiographic follow-up.

Duke Medical Center, to address this problem of incomplete angiographic follow-up study. The study group consists of a training sample of 1,069 patients randomly selected from 2,138 consecutive patients with a successful initial angioplasty procedure. All patients undergoing coronary angioplasty at Duke University were asked to return for repeat angiography at 6 months unless a contraindication was present or an intercurrent event occurred requiring catheterization before the 6 month angiographic end point. This project has resulted in successful repeat angiography in 85% of eligible patients. Using data from this group of patients, we were able to examine the effect of differential rates of angiographic follow-up study (Fig. 2). The reported restenosis rate can vary substantially, depending on how patients failing to return are included. We recommend using such adjustment techniques to estimate the possible range of *actual* restenosis rates, rather than simply relying on available data.

Noninvasive Testing

The value of a noninvasive test that could accurately and reliably detect coronary restenosis is obvious. As just reviewed, the reported value of a noninvasive test depends greatly on the completeness of angiographic follow-up data. Unfortunately, the results of noninvasive testing are frequently confounded by inadequate stress yielding low exercise heart rates, the presence of drugs that are known to influence test results and the extent of disease in vessels other than those dilated (17).

Symptoms versus stress testing (Tables 1 and 2). The value of symptoms for detecting restenosis has varied widely

Table 1. Detection of Coronary Restenosis by Exercise Treadmill Testing

Authors (ref)	No. of Pts	No. With Angiographic Follow-Up	Restenosis Rate (%)	Sens	Spec	PPV	NPV	Timing of Test
El-Tamimi et al. (21)	31	31	45	79	82	79	82	3 days
				93	100	100	94	1.3.6 mo
O'Keefe et al. (22)	48	48	13	15	86	29	73	<1 mo
Wijns et al. (23)	120	89	35	37	76	50	65	3–7 wk
Wijns et al. (26)	87	77	40	38	73	60	52	3–8 wk
Scholl et al. (24)	36	30	12	33	33	40	27	1 mo
				78	33	64	50	6 mo
Ernst et al. (25)	25	25	4	75	85	50	95	4–8 mo
Rosing et al. (18)	100	100	34	62	64	47	76	8 mo
Bengtson et al. (19)	209	200	25	60	69	61	84	6 mo
Honan et al. (20)	164	144	40	24	88	57	64	6 mo

NPV = negative predictive value; PPV = positive predictive value; Pts = patients; ref = reference; Sens = sensitivity; Spec = specificity.

among studies, although on average 60% to 70% of patients with recurrent angina have restenosis and 10% to 20% of those without recurrent symptoms have restenosis (Table 1). Exercise treadmill testing substantially improves the detection of restenosis, especially if information from the electrocardiogram (ECG) and symptomatic data are synthesized (Table 2) (18–20). Radionuclide angiography and exercise thallium studies have been reported (20–29) to have higher specificity, although substantial problems with sensitivity remain.

Several studies (23,26,30,31) have reported that an early thallium scintigraphy test with exercise, atrial pacing or dipyridamole can detect early in their course patients who will later have restenosis (Table 3). Exercise echocardiography and dipyridamole echocardiography are also used to detect restenosis (32–34). In a study (32) of 71 patients who underwent exercise echocardiography at the time of follow-up angiography, the sensitivity of a regional wall motion abnormality immediately after exercise was 71%, the specificity was 68% and the positive and negative predictive values were 53% and 82%, respectively.

Predictive value of noninvasive testing. The role of noninvasive testing in the detection of restenosis has not substantially changed over the past year. Although a positive test result is only moderately accurate in identifying patients with angiographically defined restenosis, a negative result provides a high level of assurance that restenosis is absent. The outcome of patients with angiographic restenosis who remain asymptomatic and who have no evidence of exercise-induced ischemia is uncertain, although one preliminary report (35) indicates a benign course in these patients, with occurrence of symptoms well before a clinical event. Therefore, in clinical practice "watchful waiting" until symptomatic or exercise-induced ischemia occurs appears to be reasonable.

Patient-Related Factors

Patient-related variables associated with restenosis. In a recent review and meta-analysis of available data (36), we concluded that several patient-related variables were apparently associated with restenosis. These factors included male gender, continued smoking after angioplasty, diabetes, absence of a previous myocardial infarction and unstable angina. Many other factors were found to have no association with restenosis. Additional reports (37–39) over the past year have been inconsistent, leading to greater uncertainty with regard to some risk factors and restenosis. Only diabetes, severe angina and the absence of prior infarction have consistently remained as substantial patient-related variables (37–39).

Two recent studies (38,40), both from the Cleveland Clinic, evaluated the association of multiple risk factors and restenosis. Interpretation of these studies is hindered by low

Table 2. Detection of Coronary Restenosis by Radionuclide Angiography

Author (ref)	No. of Pts	No. With Angiographic Follow-Up	Restenosis Rate (%)	Sens	Spec	PPV	NPV	Timing of Test
DePuey et al. (27)	44	19	6	83	54	45	88	0–4 days
O'Keefe et al. (22)	48	48	13	100	51	43	100	<1 mo
Ernst et al. (25)	25	25	4	100	75	44	100	4–8 mo
DePuey et al. (28)	41	41	8	88	74	54	94	4–12 mo
Rosing et al. (18)	45	45	21	75	5	15	50	8 mo

Abbreviations as in Table 1.

Table 3. Detection of Coronary Restenosis by Thallium-201 Scintigraphy

Author (ref)	No. of Pts	No. With Angiographic Follow-Up	Restenosis Rate (%)	Sens	Spec	PPV	NPV	Timing of Test
Hardoff et al. (29)	90	71	32	77	67	53	86	12–24 h
Jain et al. (30)	40	22	14	79	88	79	88	0–6 days
Lam et al. (31)	43	43	9	89	96	89	96	≤2 wk
Wijns et al. (23)	120	89	35	74	83	74	83	3–7 wk
Wijns et al. (26)	87	77	40	70	84	82	72	3–8 wk
Scholl et al. (24)	36	30	12	42	56	56	42	1 mo
				78	100	100	75	6 mo
Ernst et al. (25)	25	25	4	100	80	50	100	4–8 mo
Rosing et al. (18)	58	58	21	76	46	37	83	8 mo

Abbreviations as in Table 1.

or unknown rates of angiographic follow-up (32.4% in one study and the use of only patients with angiographic follow-up in the other). Neither of these studies identified gender as a risk factor for restenosis. These findings are consistent with the hypothesis that previously reported higher restenosis rates in men may have represented inadequate initial results in luminal reduction because of the inability of older angioplasty equipment to achieve a small residual stenosis in large coronary arteries.

Smoking. Continued smoking was not found to be related to restenosis in the Cleveland Clinic studies (38,40), thereby raising the issue of whether the previously reported small series (41) pointing to continued smoking as a risk factor in fact were not representative of the general group of patients undergoing angioplasty. This issue requires further evaluation in larger prospective studies.

Hyperlipidemia. The effect of lipids on restenosis remains controversial. Bergelson et al. (42) found a substantial relation between multiple baseline lipid measures and the risk of restenosis, including total cholesterol high density lipoprotein (HDL), low density lipoprotein (LDL), apolipoproteins A_1 and B (apo-A_1 and B) and various ratios. Linear relations between restenosis rates and apo-A_1, LDL and HDL were also found. In a separate study (43), higher serum liproprotein-a (Lp[a]) levels at follow-up were associated with restenosis. Several studies (40,43,44), however, found no relation between restenosis and lipid values at baseline or follow-up and one study (44) actually reported a lower risk of restenosis in patients with higher total cholesterol levels.

Fibrinolytic system variables and restenosis. Several small studies have now begun to investigate the relation between aspects of the fibrinolytic system and restenosis. In a study (45) of 106 patients, 36 of whom showed angiographic evidence of restenosis, an increase in plasminogen activator inhibitor-1 levels was observed after angioplasty in patients with restenosis, whereas a decrease in plasminogen activator inhibitor-1 from baseline values was observed in those without restenosis. In a smaller study (46) of greater detail but limited by its retrospective design, elevation of almost every procoagulant factor (plasminogen activator inhibitor-1, tissue plasminogen activator antigen level, fibrinogen, factors VII and VIII) and depression of inducible fibrinolytic response were observed in patients with restenosis. Several other small studies (47,48) demonstrated a release of markers of white cell activation in patients undergoing angioplasty, although no studies evaluating a possible relation to restenosis have been performed.

Role of long-term treatment with hemodialysis. Another small study (49) reported an extraordinary restenosis rate of 81% in 11 of 17 patients on long-term treatment with hemodialysis who returned for follow-up angiography after undergoing angioplasty. Whether this rate identifies dialysis itself as the primary risk factor or whether the associated metabolic abnormalities are critical remains to be determined.

In summary, surprisingly few factors have consistently been demonstrated to be associated with the risk of restenosis. The possibility remains that this finding represents an artifact of studies with inadequate measurement of risk factors and incomplete angiographic follow-up, although the evidence is increasing that the process of restenosis is distinct from that of primary atherosclerosis (50).

Lesion Morphology

Morphologic predictors of restenosis. Results from the recently completed M-HEART study (10) provide the only new data with regard to lesion morphology and its effect on restenosis. Five covariates were found to be independent predictors of restenosis in both univariate and multivariate analysis. These were stenosis location, baseline percent diameter stenosis, stenosis length, adjacent artery diameter and postangioplasty stenosis severity. The angiographic restudy rate of 73.5% combined with the sample size of the study (the highest of any pharmacologic intervention trial to date) allowed stratification of lesions into low, intermediate and high risk for restenosis. Unexpectedly, the lesions thought to be at lowest risk of restenosis tended to have a lower restenosis rate in the patients receiving methylprednisolone.

Halon et al. (39) examined 90 patients with unstable

angina undergoing coronary angioplasty for angiographic factors identifying patients at high risk for restenosis. They found that restenosis was more frequent in the left anterior descending coronary artery, in patients with multiple irregularities, in the presence of diminished Thrombolysis in Myocardial Infarction (TIMI) flow (<grade 3) and in patients with evidence of intraluminal thrombus. The authors (39) concluded that although coronary angioplasty can be performed safely in patients with unstable angina, in patients with these risk factors, restenosis may be the rule rather than the exception.

Implications. These data confirm the evolutionary phases that coronary angioplasty is undergoing with attempts to identify patients who would derive the most short-term (avoidance of procedural and in-hospital complications) and long-term (avoidance of restenosis) benefit from angioplasty. Carefully performed analyses of existing observational data bases using combined patient risk factor data and extensive acquisition of lesion morphology coupled with quantitative angiography will lay the groundwork for future interventional trials using modifications of either the procedure itself or administration of pharmacologic agents to modify cellular growth.

New Angioplasty Technologies

Over the past year, substantial information has accrued to permit the development of an initial perspective on the role of new technologies in approaching restenosis. Specific details concerning these technologies are provided elsewhere in this symposium. An overview will be provided here.

Autoperfusion device. Prolonged, slow balloon inflation has been associated with less restenosis in an animal model, prompting hope that either pretreatment with beta-adrenergic blockers, calcium channel blockers, nitrates, oxygenated fluorocarbons or retroperfusion or mechanical approaches to allow prolonged inflation would have an impact on restenosis. The development of an autoperfusion device has allowed a significantly extended balloon inflation, yielding a somewhat lower restenosis rate than that observed with standard angioplasty in a pilot study (51) of 67 patients with 90% angiographic follow-up. A multicenter randomized trial of 1 min versus 15 min inflations is currently underway, with the primary end points of immediate outcome and long-term restenosis.

Atherectomy. This procedure provides an important potential approach to restenosis because it works by physically removing the atherosclerotic plaque, often leaving a normal or nearly normal lumen, as visualized angiographically at the completion of the interventional procedure. Furthermore, creation of a more favorable rheologic environment featuring a smoother residual lumen with more normal flow characteristics might provide a further advantage in improving procedural success or reducing restenosis. However, in a recent report (52), 37 (40%) of 91 lesions developed restenosis after treatment with the Simpson Atherocath, a device that recently gained approval for use in the treatment of coronary artery disease. Similar results have been observed (53) in >70 patients returning for 6 month follow-up angiography after atherectomy with the Transluminal Extraction-Endarterectomy Catheter (TEC). These results occurred despite the typical creation of a widely patent lumen during the procedure, pointing to the probability that vascular injury overwhelms any local rheologic effect that would reduce restenosis.

Coronary stent implantation. Coronary stents also produce a widely patent artery in the immediate periprocedural interval. Unfortunately, preliminary data (54) indicate a substantial restenosis rate with all available stents, although some reported data (55) suggest that when the final stent diameter is >3.2 mm and a single stent is used (as opposed to multiple implantations), restenosis may be somewhat diminished. Careful evaluation is consistent with the concept that stent implantation can eliminate the elastic recoil component and that with the same degree of intimal proliferation, the lumen can remain widely patent in a patient after stent placement. In contrast, a significant residual stenosis would be present after angioplasty because of the lesser residual lumen at the end of the procedure. Further angiographic follow-up study is needed to clarify this issue.

Laser angioplasty. Restenosis data after laser angioplasty are preliminary at this time, but the small amount of information concerning thermal use of laser devices as a way to prevent restenosis is not encouraging. Another approach, laser balloon angioplasty (56), appears beneficial in reducing acute procedural failure, but the restenosis rate appears not to be affected by this technology (57). More recently, truly ablative laser systems have been developed using clinically powerful pulsed lasers, allowing the possibility for direct tissue ablation without pathologic heating of surrounding tissue.

In summary, the interventional mechanical approaches to coronary artery disease are evolving rapidly. Preliminary data suggest that even though tissue removal, stenting and laser ablation may have specialized applicability, these techniques do not overcome the proliferative response responsible for restenosis. Further studies with randomized comparisons are needed to assess the proper role of each of these new technologies.

Clinical Trials

Antiplatelet agents. The use of antiplatelet agents and the modulation of prostaglandin production have been a major emphasis of pharmacologic restenosis trials to date. Aspirin has been tested in seven clinical trials (58–64), but in only one study (59) was the result evaluated by quantitative angiography. When data from four clinical trials (58–61) were combined in a meta-analysis format (65), there was an insignificant 11% reduction in the risk of restenosis with aspirin (Fig. 3). When three trials (62–64) comparing high

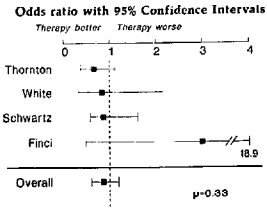
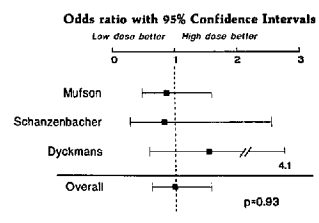


Figure 3. Overview of trials comparing aspirin therapy with placebo or control groups for restenosis after angioplasty. Results are shown as odds ratio with 95% confidence intervals, as calculated by Mantel-Haenszel statistics. An odds ratio <1 is indicative of a lower restenosis rate among the treated patients compared with placebo-treated or control patients. A statistically significant ($p < 0.05$) lower restenosis rate is seen in those studies where the 95% confidence intervals do not cross the vertical line (odds ratio = 1). Odds ratios >1 indicate a higher restenosis rate among the treated patients. Odds ratios were calculated from patients in whom angiographic documentation of restenosis were available. In those studies where angiographic data were not reported the overall numbers were used. Data are from Ohman et al. (65), Thornton et al. (58), White et al. (59), Schwartz et al. (60) and Finci et al. (61).

and low dose aspirin were combined, a trend toward a lower restenosis rate with low dose aspirin was present in two studies (62,63) (Fig. 4). In a recent study by Chesebro et al. (66), no difference in minimal luminal diameter was found among patients randomized to aspirin (975 mg/day) or placebo. Ticlopidine was evaluated in one study (59) with no apparent individual effect, but when combined with nicorandil (a calcium channel antagonist) a significant reduction was observed in the rate of restenosis compared with that during aspirin therapy (67).

Figure 4. Overview of trials comparing high dose (1,000 to 1,500 mg/day) and low dose (80 to 320 mg/day) aspirin in the prevention of restenosis after angioplasty. Results are shown as odds ratio with 95% confidence intervals. See Figure 3 for description of methods. Data are from Ohman et al. (65), Mufson et al. (62), Schanzenbacher et al. (63) and Dyckmans et al. (64).



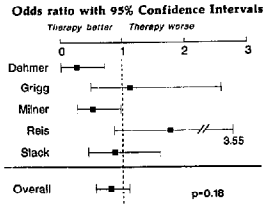


Figure 5. Overview of trials comparing omega-3 fatty acids with placebo for restenosis after angioplasty. Results are shown as odds ratio with 95% confidence intervals. Patients randomized to fish oils received 3 to 6 g/day of omega-3 fatty acids. See Figure 3 for description of methods. Data are from Ohman et al. (65), Dehmer et al. (73), Grigg et al. (74), Milner et al. (75), Reis et al. (76) and Slack et al. (77).

Prostacyclin and anticoagulants. Two relatively small studies (68,69) evaluated prostacyclin analogues and demonstrated a substantial trend toward benefit. A marked reduction in negative clinical end points was observed with ciprostene, although only a trend toward a lower rate of angiographically defined restenosis was observed (36). Anticoagulants have also been a source of recent interest. Both intravenous heparin and Coumadin (warfarin) were evaluated in relatively small trials (58,70) with low rates of angiographic follow-up and neither agent demonstrated an effect against restenosis.

Coronary vasodilators and corticosteroids. Vasodilators are generally administered to patients close to the time angioplasty is performed because of angiographic and clinical evidence of the importance of spasm as a complicating factor of angioplasty. Results of two studies (71,72) with a calcium channel antagonist were negative, although both studies included <300 patients. Because of the documented importance of smooth muscle cell proliferation in the process of restenosis, interest has intensified in the potential use of antimitogens. The M-HEART Study Group (10) recently reported on 915 patients randomly allocated to receive methylprednisolone (1 g before angioplasty) or placebo. A restenosis rate of 39% was observed in the treated patients compared with 40% in the placebo group, although a retrospective analysis suggested a beneficial effect of corticosteroids in patients with low risk angiographic characteristics for restenosis.

Fish oil preparations. The effects of fish oil preparations were examined in five studies (73–77), prompted by documentation of antiaggregatory properties on platelets, favorable alteration of lipid profiles and antimitogenic properties. Although two (73,75) of the five studies individually showed positive results, when the 725 patients involved in all the studies were evaluated as a combined group (65), an insignificant treatment effect was found (Fig. 5). The possible role

of fish oil is complicated by differences of opinion regarding dose, timing and type of patient, so that no definitive conclusion can be drawn at this time.

Serum cholesterol reduction. Two recent studies (78,79) attempted to address the potential effect of cholesterol reduction on restenosis. In one study (78), 157 patients were randomly assigned to lovastatin therapy (20 to 40 mg/day) or to a control group. Respective restenosis rates of 14% and 47% were found in the groups. This study was limited by only 50% angiographic follow-up, which was skewed toward the lovastatin group (63% versus 37%). In a separate study (79) with 93% angiographic follow-up, 55 patients were placed on a diet, lovastatin (40 to 80 mg/day) and colestipol (10 mg/day) to lower cholesterol. A 34% restenosis rate was observed, which was not different from previously reported historic control results, despite a reduction in total cholesterol from 227 to 131 mg/dl over the course of the 6 month follow-up period. With the divergent results of these two studies, it is unclear whether efforts at lowering cholesterol have any effect on restenosis.

Implications. Despite the extensive theoretic basis for the prevention of restenosis, no trials have yet demonstrated a convincing effect. Many of the previous trials have been flawed by statistical and design problems, but multiple trials are currently underway to assess each of the major areas of potential impact. These trials provide an opportunity to resolve the pathophysiologic questions because most have an adequate planned sample size and extensive data collection including qualitative and quantitative angiography.

Future Projections

Clinical trial approaches. The next year will see a proliferation of basic and clinical approaches to coronary restenosis. Because of the lack of a suitable animal model for restenosis, prevention of intimal proliferation in one species cannot be assumed to predict successful prevention of restenosis in humans. Development of a successful approach to the prevention of restenosis will depend on careful empiric clinical experimentation, attention to the details of measurement variables equated with restenosis, as well as fastidious attention to study design. Outcome should be reported with respect to both clinical and angiographic results because no single definition of restenosis is suitable. Relatively small, carefully done studies with serial quantitative angiographic measurements will provide the best information about the impact of therapy on the processes of restenosis (elastic recoil and intimal proliferation). Larger clinical trials with measurements of less precise pathoanatomic outcomes will be needed to assess the impact of the treatment as it pertains to clinical practice. One attractive approach, given the large number of angioplasty procedures currently performed, would be to perform a "megatrial" with ascertainment of a composite clinical outcome. We see these clinical trial approaches as complementary.

End points to characterize angioplasty outcome. One major problem with clinical trials involving restenosis is the small number of "hard" clinical events (death and reinfarction) that occur in patients undergoing angioplasty. We (80) developed an approach to this problem in the area of acute myocardial infarction, in which negative clinical outcomes are ranked and considered in the aggregate as a composite clinical end point. Clinicians can readily rank a similar set of end points characterizing angioplasty outcome in the following order: death, stroke, nonfatal myocardial infarction, abrupt reclosure of the dilated artery without myocardial infarction, emergency coronary bypass surgery within 24 h of angioplasty, bypass surgery >24 h after angioplasty, recurrent angina, exercise-induced silent ischemia and angiographically documented restenosis without symptoms or exercise-induced objectively documented ischemia. If patients are ranked according to the severity of these outcomes, a sensitive treatment comparison can be made in a clinically relevant manner.

Factorial design to evaluate results of treatment. Because the pathophysiology of restenosis is likely to be multifactorial, the maximal efficacy probably will be derived from combining multiple treatment approaches simultaneously, each attacking a different aspect of the pathophysiology. One possible scenario is that mechanical approaches will reduce restenosis by 20%, antithrombin agents by 20% and antiplatelet agents by 20%. Accordingly, clinical trials should ideally be designed using a factorial design. For example, a mechanical approach designed to prevent elastic recoil could be combined with an antithrombotic agent or an antiplatelet agent could be combined with an antiproliferative agent. Such a factorial design enables the study to evaluate both the individual and the combined effect of each approach, while avoiding the increased overhead cost of starting two concurrent or sequential trials.

References

1. Davies MJ, Thomas AC. Plaque fissuring: the cause of acute myocardial infarction sudden ischemic death, and crescendo angina. Br Med J 1985;53:363–73.
2. Wissler RW, Vesselinovitch D. The development and use of animal models in atherosclerotic research. In Gallo L, ed. Cardiovascular Disease '86. New York: Plenum, 1987:337–57.
3. Vesselinovitch D. Animal models and the study of atherosclerosis. Arch Pathol Lab Med 1988;112:1011–7.
4. Baumgartner HR. The role of blood flow in platelet adhesion, fibrin deposition, and formation of mural thrombi. Microvasc Res 1973;5:167–79.
5. Faxon DP, Weber VJ, Haudenschild C, Gottsman SB, McGovern WA, Ryan TJ. Acute effects of transluminal angioplasty in three experimental models of atherosclerosis. Arteriosclerosis 1982;2:125–34.
6. Gal D, Rongione AJ, Slovenkai GA, et al. Atherosclerotic Yucatan microswine: an animal model with high-grade, fibroosific, nonfatty lesions suitable for testing catheter-based interventions. Am Heart J 1990;119:291–300.
7. Serruys PW, Luijten HE, Beatt KJ, et al. Incidence of restenosis after successful coronary angioplasty: a time-related phenomenon. Circulation 1988;77:361–71.
8. Bove AA, Holmes DR, Owen RM, et al. Estimation of the effects of

angioplasty on coronary stenosis using quantitative video angiography. Cathet Cardiovasc Diagn 1985;11:5–9.
9. Liu MW, Roubin GS, King SB. Does an optimal luminal result after PTCA reduce restenosis? Circulation 1989;80(suppl II):II-63.
10. Popma CJ, Hirshfeld JW, Macdonald RG, et al. A controlled trial of corticosteroids to prevent restenosis after coronary angioplasty. Circulation 1990;81:1753–61.
11. Rensing BJ, Serruys PW, Beatt KJ, Suryapranata H, Laarman GJ, de Feyter PJ. Densitometrically observed differences in elastic recoil of the three main coronary arteries after percutaneous transluminal coronary angioplasty (abstr). J Am Coll Cardiol 1990;15:45A.
12. Nobuyoshi M, Takeshi K, Nosaka H, et al. Restenosis after successful percutaneous transluminal coronary angioplasty: serial angiographic follow-up of 229 patients. J Am Coll Cardiol 1988;12:616–23.
13. Kalbfleisch SJ, McGillem MJ, Pinto IMF, Kavanaugh KM, DeBoe SF, Mancini J. Comparison of automated quantitative coronary angiography with caliper measurements of percent diameter stenosis. Am J Cardiol 1990;65:181–4.
14. Reiber JHC, Serruys PW, Kooijman CJ, et al. Assessment of short-, medium-, and long-term variations in arterial dimensions from computer-assisted quantitation of coronary cineangiograms. Circulation 1985;71:280–8.
15. Beatt KJ, Luijten HE, de Feyter PJ, van den Brand M, Reiber JH, Serruys PW. Change in diameter of coronary artery segments adjacent to stenosis after percutaneous transluminal coronary angioplasty: failure of percent diameter stenosis measurement to reflect morphologic changes induced by balloon inflation. J Am Coll Cardiol 1988;12:315–23.
16. Gurley JC, Nissen SE, Haynie D, Sublett K, Booth DC, DeMaria AN. Is routine automated quantitative analysis of coronary arteriography feasible? Evaluation of operator-dependent variables inherent to the technique (abstr). J Am Coll Cardiol 1990;15:115A.
17. Hlatky MA, Mark DB. Overview of diagnostic test assessment. In: Califf RM, Mark DB, Wagner GS, eds. Acute Coronary Care in the Thrombolytic Era. Chicago: Year Book Medical, 1988:91–9.
18. Rosing DR, Van Raden MJ, Mincemoyer RM, et al. Exercise electrocardiographic and functional responses after percutaneous transluminal coronary angioplasty. Am J Cardiol 1984;53:36C–41C.
19. Bengtson JR, Mark DB, Honan MB, et al. Detection of restenosis after elective percutaneous transluminal coronary angioplasty using the exercise treadmill test. Am J Cardiol 1990;65:28–34.
20. Honan MB, Bengtson JR, Pryor DB, et al. Exercise treadmill testing is a poor predictor of anatomic restenosis after angioplasty for acute myocardial infarction. Circulation 1989;80:1585–94.
21. El-Tamimi H, Davies GJ, Hackett D, et al. Very early prediction of restenosis after successful coronary angioplasty: anatomic and functional assessment. J Am Coll Cardiol 1990;15:259–64.
22. O'Keefe JH, Lapeyre AC, Holmes DR, Gibbons RJ. Usefulness of early radionuclide angiography for identifying low-risk patients for late restenosis after percutaneous transluminal coronary angioplasty. Am J Cardiol 1988;61:51–4.
23. Wijns W, Serruys PW, Reiber JHC, et al. Early detection of restenosis after successful percutaneous transluminal coronary angioplasty by exercise-redistribution thallium scintigraphy. Am J Cardiol 1985;55:557–61.
24. Scholl JM, Chaitman BR, David PR, et al. Exercise electrocardiography and myocardial scintigraphy in the serial evaluation of the results of percutaneous transluminal coronary angioplasty. Circulation 1982;66:380–90.
25. Ernst SMPG, Hillebrand FA, Klein B, Aspoop CA, van Tellingen C, Plokker HWM. The value of exercise tests in the follow-up of patients who underwent transluminal coronary angioplasty. Int J Cardiol 1985;7:267–79.
26. Wijns W, Serruys PW, Simoons ML, et al. Predictive value of early maximal exercise test and thallium scintigraphy after successful percutaneous transluminal coronary angioplasty. Br Heart J 1985;53:194–200.
27. DePuey EG, Boskovic D, Krajcer Z, et al. Exercise radionuclide ventriculography in evaluating successful transluminal coronary angioplasty. Cathet Cardiovasc Diagn 1983;9:153–66.
28. DePuey EG, Leatherman LL, Leachman RD, et al. Restenosis after transluminal coronary angioplasty detected with exercise-gated radionuclide ventriculography. J Am Coll Cardiol 1984;4:1103–13.
29. Haudoff R, Shefer A, Gips S, et al. Predicting late restenosis after coronary angioplasty by very early (12 to 24 h) thallium-201 scintigraphy: implications with regard to mechanisms of late coronary restenosis. J Am Coll Cardiol 1990;15:1486–92.
30. Jain A, Mahmarian JJ, Boges-Neto S, et al. Clinical significance of perfusion defects by thallium-201 single photon emission tomography following oral dipyridamole early after coronary angioplasty. J Am Coll Cardiol 1988;11:970–6.
31. Lam JYT, Chaitman BR, Byers S, et al. Can dipyridamole thallium imaging predict restenosis after coronary angioplasty? (abstr). Circulation 1987;76(suppl IV):IV-373.
32. Bengtson JR, Sheikh KH, Abdul-Enein H, Burgess R, Stack RS, Kisslo J. Exercise echocardiography is a valuable adjunct to treadmill testing for detection of restenosis after coronary angioplasty (abstr). J Am Coll Cardiol 1990;15(suppl A):52A.
33. Rowland AJ, Ridzwick S, Beauchamp GD, et al. Exercise echocardiography correctly predicts restenosis in patients undergoing emergent PTCA for non-Q wave myocardial infarction (abstr). J Am Coll Cardiol 1990;15(suppl A):52A.
34. Picano E, Pirelli S, Marzilli M, et al. Usefulness of high-dose dipyridamole echocardiography test in coronary angioplasty. Circulation 1989;80:807–15.
35. Popma JJ, van den Berg EK, Dehmer GJ. Long-term outcome of patients with asymptomatic restenosis after percutaneous coronary angioplasty. Am J Cardiol 1988;62:1298–9.
36. Califf RM, Ohman EM, Frid DJ, et al. Restenosis: the clinical issues. In: Topol EJ, ed. Interventional Cardiology. Philadelphia: WB Saunders, 1989:363–94.
37. Margolis JR, Chen C, Glemser E. Restenosis after PTCA is increased in diabetic patients (abstr). Eur Heart J 1989;10(suppl III):III-5.
38. Hollman J, Badhwar K, Beck GJ, Franco I, Simpfendorfer C. Risk factors for recurrent stenosis following successful coronary angioplasty. Cleve Clin J Med 1989;56:517–23.
39. Halon DA, Merdler A, Shefer A, Flugelman MY, Lewis BS. Identifying patients at high risk for restenosis after percutaneous transluminal coronary angioplasty for unstable angina pectoris. Am J Cardiol 1989;64:289–93.
40. Arora RR, Konrad K, Badhwar K, Hollman J. Restenosis after transluminal coronary angioplasty: a risk factor analysis. Cathet Cardiovasc Diagn 1990;19:17–22.
41. Galan KM, Deligonul L, Kern MJ, Chaitman BR, Vandormael MG. Increased frequency of restenosis in patients continuing to smoke cigarettes after percutaneous transluminal coronary angioplasty. Am J Cardiol 1988;61:260–3.
42. Bergelson BA, Jacobs AK, Small DM. Lipoproteins predict restenosis after PTCA (abstr). Circulation 1989;80(suppl II):II-65.
43. Hearn JA, Donohue BC, King SB, et al. Does serum LP(a) predict restenosis after PTCA? (abstr). J Am Coll Cardiol 1990;15(suppl A):205A.
44. Austin GE, Hollman J, Lynn MJ, Meier B. Serum lipoprotein levels fail to predict postangioplasty recurrent coronary artery stenosis. Cleve Clin J Med 1989;56:609–14.
45. Huber K, Jorg M, Resch I, et al. Association of a significant increase of plasminogen activator inhibitor-1 with the development of coronary restenosis in patients after PTCA (abstr). J Am Coll Cardiol 1990;15:209A.
46. Kirschstein W, Simianer S, Dempfle CE, et al. Impaired fibrinolytic capacity and tissue plasminogen activator release in patients with restenosis after percutaneous transluminal coronary angioplasty (PTCA). Thromb Haemost 1989;62:772–5.
47. de Servi S, Ricevuti G, Mazzone A, et al. Neutrophil activation after PTCA in humans (abstr). Circulation 1989;80(suppl II):II-260.
48. Steg PG, Pasquier C, Pham T, et al. Evidence for neutrophil and complement activation early after PTCA (abstr). J Am Coll Cardiol 1990;15(suppl A):164A.
49. Kahn JK, Rutherford BD, McConahay DR, Johnson WL, Giorgi LV, Hartzler GO. Short- and long-term outcome of percutaneous transluminal coronary angioplasty in chronic dialysis patients. Am Heart J 1990;119:484–9.
50. Schwartz RS, Murphy JG, Edwards WD, Reiter SJ, Vlietstra RE, Holmes DR. A practical porcine model of human coronary artery restenosis post PTCA (abstr). J Am Coll Cardiol 1990;15(suppl A):165A.
51. Quigley PJ, Kereiakes DJ, Abbotsmith CW, et al. Prolonged autoperfusion angioplasty: immediate clinical outcome and angiographic follow-up. J Am Coll Cardiol 1989;13(suppl A):155A.

52. Hinohara T, Rowe M, Sipperly ME, et al. Restenosis following directional coronary atherectomy of native coronary arteries (abstr). J Am Coll Cardiol 1990;15(suppl A):196A.
53. Stack RS, Phillips HR, Quigley PJ, et al. Multicenter registry of coronary atherectomy using the transluminal extraction-endarterectomy catheter (abstr). J Am Coll Cardiol 1990;15(suppl A):196A.
54. Serruys PW, Beatt KJ, Bertrand M on behalf of the Working Group of Endoluminal Coronary Artery Prostheses. Restenosis rate after coronary stent implantation: angiographic assessment of the initial series (abstr). Circulation 1989;80(suppl II):II-690.
55. Ellis SG, Savage MP, Leon MB, et al. Intracoronary stenting to prevent restenosis: preliminary results of a multicenter study using the Palmaz-Schatz stent suggest benefit in selected high risk patients (abstr). J Am Coll Cardiol 1990;15(suppl A):118A.
56. Litvack F, Margolis J, Eigler N, et al. Percutaneous excimer laser coronary and angioplasty: results of the first 110 procedures (abstr). J Am Coll Cardiol 1990;15(suppl A):25A.
57. Ferguson JJ, Dear WE, Leatherman LL, et al. A multi-center trial of laser balloon angioplasty for abrupt closure following PTCA (abstr). J Am Coll Cardiol 1990;15(suppl A):25A.
58. Thornton MA, Gruentzig AR, Hollman J, King SB, Douglas JS, Coumadin and aspirin in prevention of recurrence after transluminal coronary angioplasty: a randomized study. Circulation 1984;69:721–7.
59. White CW, Knudson M, Schmidt RJ, et al. Neither ticlopidine nor aspirin-dipyridamole prevents restenosis post PTCA: results from a randomized placebo-controlled multicenter trial (abstr). Circulation 1987; 76(suppl IV):IV-213.
60. Schwartz L, Bourassa MG, Lesperance J, et al. Aspirin and dipyridamole in the prevention of restenosis after percutaneous transluminal coronary angioplasty. N Engl J Med 1988;318:1714–9.
61. Finci L, Meier B, Steffenio G, Rutishauser W. Aspirin versus placebo after coronary angioplasty for prevention of restenosis (abstr). Eur Heart J 1988;9(suppl I):156.
62. Mufson L, Black A, Roubin G, et al. A randomized trial of aspirin in PTCA: effect of high vs low dose aspirin on major complications and restenosis (abstr). J Am Coll Cardiol 1988;11(suppl A):236A.
63. Schanzenbacher P, Grimmer M, Maish B, Kochsiek K. Effect of high dose and low dose aspirin on restenosis after primary successful angioplasty (abstr). Circulation 1988;78(suppl II):II-98.
64. Dyckmans J, Thonnes W, Ozbek C, et al. High vs low dosage of acetylic salicylic acid for prevention of restenosis after successful PTCA: preliminary results of a randomized trial (abstr). Eur Heart J 1988;9(suppl I):58.
65. Ohman EM, Califf RM, Lee KL, Fortin DF, Frid DJ, Bengtson JR. Restenosis after angioplasty: overview of clinical trials using aspirin and omega-3 fatty acids (abstr). J Am Coll Cardiol 1990;15(suppl A):88A.
66. Chesebro JH, Webster MWI, Reeder GS, et al. Coronary angioplasty: antiplatelet therapy reduces acute complications but not restenosis (abstr). Circulation 1989;80(suppl II):II-64.
67. Kitazume H, Kubo I, Iwama T, Ageishi Y, Suzuki A. Combined use of aspirin, ticlopidine and nicorandil prevented restenosis after coronary angioplasty (abstr). Circulation 1988;78(suppl II):II-633.
68. Knudson ML, Flintoft VA, Roth DL, Hansen JL, Duff HJ. Effect of short-term prostacyclin administration on restenosis after percutaneous transluminal coronary angioplasty. J Am Coll Cardiol 1990;15:691–7.
69. See J, Sheil W, Matthews O, et al. Prostaglandin E1 infusion after angioplasty in humans inhibits abrupt occlusion and early restenosis. Adv Prostaglandin Thromboxane Leukotriene Res 1987;17A:266–70.
70. Ellis SG, Roubin GS, Wilentz J, Douglas JS, King SB III. Effect of 18- to 24-hour heparin administration for prevention of restenosis after uncomplicated coronary angioplasty. Am Heart J 1989;117:777–82.
71. Corcos T, David PR, Val PG, et al. Failure of diltiazem to prevent restenosis after percutaneous transluminal coronary angioplasty. Am Heart J 1985;109:926–31.
72. Whitworth HB, Roubin GS, Hollman J, et al. Effect of nifedipine on recurrent stenosis after percutaneous transluminal coronary angioplasty. J Am Coll Cardiol 1986;8:1271–6.
73. Dehmer GJ, Popma JJ, van den Berg EK, et al. Reduction in the rate of early restenosis after coronary angioplasty by a diet supplemented with n-3 fatty acids. N Engl J Med 1988;319:733–40.
74. Grigg LE, Kay TWH, Valentine PA, et al. Determinants of restenosis and lack of effect of dietary supplementation with eicosapentaenoic acid on the incidence of coronary artery restenosis after angioplasty. J Am Coll Cardiol 1989;13:665–72.
75. Milner MR, Gallimo RA, Leffingwell A, et al. Usefulness of fish oil supplements in preventing clinical evidence of restenosis after percutaneous transluminal coronary angioplasty. Am J Cardiol 1989;64:294–9.
76. Reis GJ, Sipperly ME, McCabe CH, et al. Randomized trial of fish oil for prevention of restenosis after coronary angioplasty. Lancet 1989;2:177–81.
77. Slack JD, Pinkerton CA, VanTassel J, et al. Can oral fish oil supplement minimize restenosis after percutaneous transluminal coronary angioplasty? (abstr). J Am Coll Cardiol 1987;9(suppl A):64A.
78. Sahni R, Maniet AR, Voci G, Banka VS. Prevention of restenosis by lovastatin (abstr). Circulation 1989;80(suppl II):II-65.
79. Hollman J, Konrad K, Raymond R, Whitlow P, Michelak M, Van Lente F. Lipid lowering for the prevention of recurrent stenosis following coronary angioplasty (abstr). Circulation 1989;80(suppl II):II-65.